REMARKS

Claims 1-21 are pending in the subject application. Applicants have hereinabove cancelled claims 1 and 2 and non-elected claims 7-18 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims at a later date. Applicants have also amended claims 19 and 21 to remove the references therein to nonelected claims 7 and 9, and to substitute "pharmaceutically" for "therapeutically." Applicants maintain that amended claims 19 and 21 do not raise any issue of new matter since the amendments merely incorporate the subject matter of original claims 7 and 9, and also the substituted term "pharmaceutically effective amount" is defined in the specification (page 16, lines 16-21). Accordingly, applicants respectfully request entry of this Amendment. Upon entry of this Amendment, claims 3-6 and 19-21, as amended, will be pending and under examination.

Election/Restriction

Applicants acknowledge the Examiner's acknowledgement of applicants' election with traverse of Group I, claims 1-6 and 19-21, her conclusion that the traversal was not persuasive, and her making of the restriction requirement final.

Objection to the Specification

The Examiner objected to the disclosure because a sentence on page 10, line 24 does not end with a period, raising the possibility that additional text is missing. In response, applicants have hereinabove inserted a period at the end of the identified sentence, thereby indicating that no additional text

was missing. Applicants respectfully submit that this amendment obviates the above-stated objection and request that the objection be withdrawn.

Objections to the Claims

The Examiner objected to claims 19 and 21 because they both reference non-elected claims 7 and 9. In response, applicants have hereinabove amended claims 19 and 21 to remove the references therein to nonelected claims 7 and 9. Accordingly, applicants respectfully request that the objection be withdrawn.

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner rejected 1-6 and 19-21 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner alleged that the specification does not reasonably provide enablement for the administration of any chemical compound, novel structural and functional analog or homolog, nor is there guidance as to how to make these molecules.

In response, applicants note that claims 1 and 2 have been cancelled, rendering the rejection thereof moot. In addition, applicants respectfully traverse the Examiner's rejection of claims 3-6 and 19-21. Applicants maintain that the instant method-of-treatment claims, as amended, comprise multiple steps, each of which is enabled by the specification.

The first step involves identifying a chemical compound that

increases intracellular cyclin-dependent kinase inhibitor p27 activity (and that consequently inhibits cellular migration). Methods for identifying such a chemical compound are detailed in claim 19, as amended, and are clearly described in the specification (see, e.g., page 19, line 27-page 20, line 7, and page 20, line 21-page 21, line 13 for methods of contacting cells with chemical agents; page 21, line 20-page 22, line 9, and page 23, lines 16-20 for a method of estimating the intracellular level of p27 activity by assaying p27 protein levels). Applicants further note that nowhere is the "making" of compounds required to practice the instant methods. Rather, using compounds is all that is required.

Regarding the Examiner's contention that there is no guidance as to how to make the structural and functional analogs or homologs of the identified chemical compound, applicants note that structural and functional analogs or homologs are not recited in the claims as amended.

In support of the rejection, the Examiner contended that the products of the homologs and analogs may possess function that is not commensurate with the functions stated in the method claims, i.e., increasing intracellular p27 activity and inhibiting cellular migration, and that these molecules might not maintain the activities proposed in the specification.

In response, applicants again note that no such language appears in the claims as amended.

The Examiner stated that there appears to be no nexus between applicants' method of treating a subject with cardiovascular disease and tumor metastasis by administering "undefined"

chemical compounds, and further that the specification exemplifies no examples of the effective use of "arbitrary" chemical compounds as therapeutic pharmacological agents for the treatment of any particular cancer or any specific cardiovascular disease.

In response, applicants respectfully refute the categorization of compounds identified to inhibit cellular migration, and their structural and functional analogs or homologs, as "undefined" or "arbitrary" compounds. This point is addressed more fully below in responding to the Examiner's rejection of claims 3, 5, 19 and 21 under 35 U.S.C 112, second paragraph.

The Examiner also alleged that it would require undue experimentation by one skilled in the art to apply a method of treatment to a human based on the teachings of a method of treating a non-human animal. In response, applicants respectfully refute this assertion on the ground that it is standard practice and essentially *de rigueur* in the pharmaceutical industry for therapeutics to be extensively tested in non-human animal systems before being applied to treatment of humans. Protocols for animal testing of therapeutics and subsequent application for human use based on such testing are well known in the art, and it is simply incorrect to assert that these procedures require undue experimentation. The Examiner has not properly set forth art indicating otherwise. Moreover, applicants contend that application of a method of treatment to a human, based on the teachings of a method of treating a non-human animal, is not a requirement of patentability. In this regard, the Examiner's attention is directed to *In Re Brana* (51 F.3d 1560, 1567, 34 U.S.P.Q.2d 1436, 1442, Fed. Cir. 1995, *per* Plager, Circuit Judge):

> The Commissioner counters that such in vivo tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means in vivo testing in humans, and therefore not reasonably predictive of the success of the claimed compounds for treating cancer in humans. The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

In view of the above remarks, applicants maintain that claims 3-6 and 19-21 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1-6 and 19-21 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner alleged that various terms and phrases, as identified below, were vague and indefinite. Applicants again note that claims 1 and 2 are cancelled.

The Examiner stated that the recitation "cell" in claim 1 is vague and indefinite as it is not clear what type of cell is affected by the increase of the intracellular cyclin-dependent kinase inhibitor p27 activity, nor is it clear if this cell is isolated, created by nature or man made.

In response, applicants note that this rejection is moot in view of the cancellation of claim 1

The Examiner also stated that claims 3, 5, 19 and 21 are vague and indefinite in the recitations "compound" and "chemical compound". The Examiner alleged that the metes and bounds of these claims cannot be determined because a "compound" can be anything, such as a peptide, an organic molecule, an inorganic molecule, a DNA fragment, a plastic, a carbohydrate, etc.

In response, applicants point out that, contrary to the statements of the Examiner, a "compound" in the context of the instant claims is not without metes and bounds because the claims do not recite the administration of any arbitrary compound. Instead, the kind of compound to be used is clearly qualified. Thus, in claims 3 and 5, the compound to be administered is one which increases intracellular cyclin-dependent kinase inhibitor p27 activity. This functional requirement clearly defines the boundaries of the compound and thus the claim, since any compound which possesses the property of causing an increase in intracellular cyclin-dependent kinase inhibitor p27 activity would fall within the metes and bounds of the type of compound to be used in the claimed invention. It would be immaterial whether that compound was, for example, a peptide or a carbohydrate. Similarly, in claims 19 and 21, the "chemical compound" to be administered is one that has been identified by specified methods as having the property of inhibiting cell migration. Again, having defined the chemical compound in specific functional terms, the chemical nature of that compound is immaterial.

The Examiner also contended that the phrase "alleviating the subject's cardiovascular disease" in claim 3 is vague and

indefinite, that it is not clear from the claim how the subject's cardiovascular disease would be lessened or relieved, and further that the metes and bounds cannot be determined absent an accurate description.

Applicants point out, in response, that the claims must be read in light of the specification which clearly indicates how a subject's cardiovascular disease would be lessened or relieved. For example, page 1, line 23 - page 2, line 1 explains that vascular smooth muscle cell (SMC) migration plays a major role in the pathogenesis of many vascular diseases, such as atherosclerosis and restenosis after both percutaneous transluminal angioplasty (PTCA) and coronary stenting, and that whereas in normal blood vessels, the majority of SMC are quiescent and reside in the media of the vessel, in disease states SMCs migrate from the media to the intima of the blood vessel. Furthermore, the publication by Poon et al. [(1996) J. Clin. Invest. 10: 2277-2283], which is incorporated by reference into the instant application, emphasizes (page 2280) that SMC migration is an important component of the intimal thickening after PCTA since SMCs necessarily have to migrate from the media into the intima to before they can proliferate and cause luminal narrowing. Page 2, lines 18-23 and lines 30-33 of the specification indicate that rapamycin inhibits both SMC proliferation and SMC migration *in vitro* and *in vivo*. Page 3, lines 8-22 suggest that rapamycin may have important applications in the treatment of disorders such as accelerated arteriopathy that occurs in transplanted hearts and restenosis after percutaneous transluminal angioplasty and placement of coronary stents. This section further cites experimental demonstrations of the efficacy of rapamycin in significantly inhibiting neointimal proliferation in a porcine angioplasty model,

reversing chronic graft vascular disease in a rodent heart allograft model, treating stent restenosis. These are clearly examples of how cardiovascular disease may be alleviated by treatment with rapamycin.

The present application discloses that the anti-migratory effects of rapamycin are mediated via the cyclin-dependent kinase inhibitor, $p27^{kip1}$, and claim 3 provides a method of treating a subject's cardiovascular disease by increasing intracellular cyclin-dependent kinase inhibitor p27 activity, thereby alleviating the subject's cardiovascular disease. Read in light of the specification, it is clear that the phrase "alleviating the subject's cardiovascular disease" includes reducing the occurrence of accelerated arteriopathy that occurs in transplanted hearts, inhibiting SMC migration from the media to the intima and consequently inhibiting neointimal proliferation in angioplasty, reversing chronic graft vascular disease, and reducing the occurrence of restenosis after percutaneous transluminal angioplasty and placement of coronary stents. Applicants submit, therefore, that contrary to the Examiner's position, it is clear in claim 3 how the subject's cardiovascular disease would be lessened or relieved, and thus the metes and bounds of the claim are clear.

The Examiner further stated that claims 19 and 21 are vague and indefinite in the recitation "therapeutically effective amount" when the claims fail to state the function which is to be achieved.

In response, applicants maintain that the function to be achieved, that of alleviating the subject's cardiovascular disease, is clearly identified in the specification as discussed

hereinabove. However, to expedite prosecution of the subject application and without conceding the correctness of the Examiner's position, applicants have hereinabove amended claims 19 and 21 to substitute "pharmaceutically effective amount" for "therapeutically effective amount." Applicants submit that this substitution obviates the Examiner's rejection as the term "pharmaceutically effective amount" is defined on page 16, lines 16-21 of the specification.

The Examiner also stated that the terms "novel structural and functional analog" and "homolog" in claims 19 and 21 are vague and indefinite. The Examiner asserted that it is not clear what is meant by the terms, and it is not clear how similar or different the analogs and homologs are in comparison to the chemical compounds capable of treating cardiovascular disease and inhibiting tumor metastasis.

In response, applicants again note that these terms are not recited in amended claims 19 and 21.

In view of the above remarks, applicants maintain that claims 3-6 and 19-21 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §102(b)

The Examiner rejected claims 1, 2 and 6 under 35 U.S.C. §102(b) as allegedly anticipated by Horiuchi et al. [(1999) Molecular Human Reproduction 5: 139-45]. Applicants again note that claims 1 and 2 have been cancelled.

Recognizing that Horiuchi et al. (1999) is directed to the

inhibition of SMC proliferation whereas the subject application provides methods for inhibiting SMC migration, the Examiner suggested that it is reasonable to conclude that concurrent with the inhibition of cell growth is the prevention of cell migration, and stated further that inherently the increase/enhancement of the cyclin-dependent kinase inhibitor p27 is due to the increase of C3 exoenzyme activity.

In response, applicants respectfully traverse and respectfully refute both these statements. Firstly, as a general point, applicants note that cell proliferation and cell migration are clearly distinct phenomena. "Cell proliferation" is an "increase in cell number by division" whereas "cell migration" is the "movement of a population of cells from one place to another – as in the movement of neural crest cells during morphogenesis." (see Dictionary of Cell and Molecular Biology, J.M. Lackie and J.A.T. Dow eds., 3rd edn., 1999, Academic Press, London; accessible online at http://www.mblab.gla.ac.uk/~julian/Dict.html). (Applicants assume that the Examiner uses the term "cell growth" as a synonym for "cell proliferation," consistent with the tendency noted by the Dictionary of Cell and Molecular Biology that "cell growth" is "usually used to mean increase in the size of a population of cells though strictly should be reserved for an increase in cytoplasmic volume of an individual cell.")

Secondly, with respect to the specific effects of $p27^{kip1}$ on SMC proliferation and migration, applicants maintain that prior to obtaining the data disclosed in the subject application, it had not been ascertained that $p27^{kip1}$ had an anti-migratory effect in cells and the discovery of this effect, in addition to the known anti-proliferative effect of $p27^{kip1}$, was unexpected. The novelty of the discovery is supported by statements in the specification

that "[t]his intriguing finding [that rapamycin and C3 exoenzyme inhibit smooth muscle cell migration through $p27^{kipl}$-dependent and -independent pathways] implicates $p27^{kipl}$ in the signaling pathway(s) that regulate both SMC proliferation and migration" (page 31, lines 19-21; emphasis added) and "[t]he findings disclosed in the present application suggest that agents that increase $p27^{kipl}$ activity *in vivo* may have both an anti-proliferative and antimigratory effect" (page 27, lines 19-22).

Thirdly, and most significantly, the specification discloses experimental results showing that a rapamycin-induced increase in $p27^{kipl}$ activity inhibits cell migration in the absence of any effect on cell proliferation (see page 23, lines 21-27). These data directly disprove the Examiner's contention that the prevention of cell migration necessarily occurs concurrently with the inhibition of cell proliferation. This factual conclusion drawn by the Examiner is therefore without merit. Indeed, the Examiner has failed to set forth any art teaching such a relationship, which is not surprising as no such relationship exists.

Applicants emphasize that the distinct and separable effects of increased $p27^{kipl}$ activity on cell proliferation and migration have important therapeutic implications. For example, restenosis requires vascular SMCs to both migrate from the media to the intima, and then once in the intima, to proliferate. Applicants' findings that $p27^{kipl}$ elevation inhibits both migration and proliferation were unexpected but are extremely important because agents that inhibit one and not the other are likely to be of limited clinical benefit.

Regarding the Examiner's assertion that the increase/enhancement

of the cyclin-dependent kinase inhibitor p27 is inherently due to an increase of C3 exoenzyme activity, applicants direct the Examiner to Figure 5 and page 11, lines 14-29 of the specification which clearly indicate that $p27^{kipl}$ activity is enhanced by rapamycin-FKBP12 which inhibits TOR-mediated down-regulation of $p27^{kipl}$. These cited references, together with page 25, line 15 to page 26, line 5 and page 28, lines 6-15, further indicate that C3 exoenzyme also enhances $p27^{kipl}$ activity but this is achieved via ADP-ribosylation and inactivation of RhoA, resulting in the inhibition of a distinctive Ras/RhoA-mediated mitogenic pathway that regulates the destruction of $p27^{kipl}$. Applicants respectfully submit, therefore, that the Examiner's contention that the increase/enhancement of the cyclin-dependent kinase inhibitor p27 is inherently due to an increase of C3 exoenzyme activity is without merit.

The Examiner also rejected claims 1, 3-6 and 19-21 under 35 U.S.C. §102(b) as allegedly anticipated by WO 99/65939. Applicants again note that claim 1 has been cancelled.

Cognizant of the fact that WO 99/65939 is directed solely to methods of inhibiting cell <u>proliferation</u>, whereas the subject application provides methods for inhibiting cell <u>migration</u>, the Examiner repeated her conclusion that concurrent with the inhibition of cell growth is the prevention of cell migration, and that inherently the increase/enhancement of the cyclin-dependent kinase inhibitor p27 is due to the increase of C3 exoenzyme activity.

Applicants respectfully traverse and maintain that these conclusions are incorrect for the reasons discussed above.

The Examiner also rejected claims 1-4, 6, 19 and 20 under 35 U.S.C. §102(b) as allegedly anticipated by WO 99/03508. Applicants again note that claims 1 and 2 have been cancelled.

The reference cited by the Examiner is directed exclusively to arresting cell growth, and again the Examiner based her rejection on her conclusion that concurrent with the inhibition of cell growth is the prevention of cell migration, and also that the increase/enhancement of the cyclin-dependent kinase inhibitor p27 is inherently due to the increase of C3 exoenzyme activity.

Applicants respectfully traverse and submit that the Examiner's rejection is without merit for the reasons discussed hereinabove.

The Examiner also rejected claims 1 and 2 under 35 U.S.C. §102(b) as allegedly anticipated by Poon et al. (1996) which discloses that rapamycin inhibits vascular SMC proliferation and migration.

In response, applicants note that claims 1 and 2 have been cancelled, rendering the Examiner's rejection thereof mute.

In view of the above remarks, applicants maintain that claims 3-6 and 19-21 satisfy the requirements of 35 U.S.C. §102(b).

Conclusion

In view of the remarks made herein, applicants respectfully request that the Examiner withdraw the various grounds of objection and rejection set forth in the February 24, 2003 Office Action and earnestly solicit allowance of all claims pending in the subject application.

If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Assistant Commissioner for Patents
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5/27/03

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